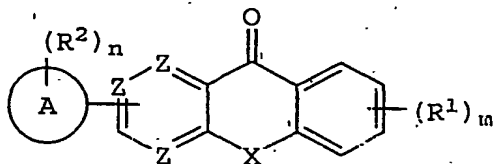


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WHAT IS CLAIMED IS:

1. A DNA-PK inhibitor having a formula



or a pharmaceutically acceptable salt thereof,

wherein m is an integer 0 through 3;

n is an integer 0 through 4;

X is O, S(O)₀₋₂, or NR^a;

Z, independently, is CR^b or N;

A is heteroaryl or a four- to seven-membered aliphatic ring containing 0, 1, 2, or 3 heteroatoms independently selected from the group consisting of N, O, and S;

R¹, independently, is selected from the group consisting of halo, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, N(R^d)₂, OR^d, carboxyl, carboxy, nitro, OC₁₋₃alkyleneN(R^d)₂, N(R^d)-C₁₋₃alkyleneN(R^d)₂, OC₁₋₃alkyleneC(=O)OR^d, O(C₁₋₃alkylene)OP(=O)(OR^d)₂, O(C₁₋₃alkylene)OP(=O)(ONa)₂, OP(=O)(OR^d)₂, OP(=O)(ONa)₂, cyano, aldehyde, carboxamide, thiocarboxamide, acyl, mercapto, sulfonyl, trifluoromethyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or

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two R^1 groups are taken together with the atoms to which each is attached to form a 5-, 6-, or 7-membered ring, wherein 1 or 2 carbon atoms of R^1 optionally is a heteroatom selected from the group consisting of O, N, and S, said ring optionally substituted with one or more =O, =S, =NH, OR^c , $N(R^d)_2$, carboxyl, carboxy, alkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, said heteroatom optionally substituted with a group selected from the group consisting of aryl, substituted aryl, alkyl, substituted alkyl, and acyl;

R^2 , independently, is selected from the group consisting of OR^d , halo, $N(R^d)_2$, aldehyde, alkyl, substituted alkyl, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_{1-3} alkylene OR^d , $C(=O)N(R^d)_2$, $N(R^d)_2$, $(C=O)OR^d$, NO_2 , $NR^dC(=O)R^d$, $NR^d(SO_2)R^d$, OC_{1-3} alkylene OR^d , OC_{1-3} alkylene OC_{1-3} alkylene R^d , $OC(=O)R^d$, OC_{1-3} alkylene $C(=O)C_{1-3}$ alkylene R^d , and $(SO_3)R^d$;

R^a is selected from the group consisting of hydro, C_{1-4} alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, C_{1-3} alkylenearyl, C_{1-3} alkyleneheteroaryl, C_{1-3} alkyleneheterocycloalkyl, C_{1-4} alkylene $N(R^d)_2$, C_{1-4} alkylene OR^d , C_{1-4} alkylene $C(=O)OR^d$, $C(=O)R^d$, $C(=O)N(R^d)_2$, $C(=O)OR^d$, $C(=O)SR^d$, $C(=S)N(R^d)_2$, SO_2R^d , $SO_2N(R^d)_2$, $C(=O)NR^dC_{1-4}$ alkylene OR^d , $C(=O)NR^dC_{1-4}$ alkyleneheterocycloalkyl, $C(=O)C_{1-4}$ alkylenearyl, $C(=O)C_{1-4}$ alkyleneheteroaryl, C_{1-4} alkylene $C(=O)C_{1-4}$ alkylenearyl,

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C_{1-4} alkyleneC(=O) C_{1-4} alkyleneheteroaryl, C_{1-4} alkyleneC(=O)heterocycloalkyl, C_{1-4} alkyleneNR^dC(=O)R^d, C_{1-4} alkyleneOC C_{1-4} alkyleneOR^d, C_{1-4} alkyleneOC C_{1-4} alkyleneC(=O)OR^d, and C_{1-4} alkyleneC(=O)N(R^d)₂;

R^b, independently, is selected from the group consisting of hydro, alkyl, halo, aldehyde, OR^d, O(C C_{1-3} alkylene)OP(=O)(OR^d)₂, O(C C_{1-3} alkylene)OP(=O)(ONa)₂, OP(=O)(OR^d)₂, OP(=O)(ONa)₂, nitro, N(R^d)₂, carboxyl, carboxy, sulfonamido, sulfamyl, and sulfo or a halide derivative thereof; and

R^d, independently, is selected from the group consisting of hydro, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, C_{1-3} alkylenearyl, substituted aryl, heteroaryl, and substituted heteroaryl.

2. The inhibitor of claim 1 wherein A is selected from the group consisting of pyridyl, morpholinyl, piperazinyl, thiomorpholinyl, piperidinyl, and tetrahydropyranyl.

3. The inhibitor of claim 1 wherein m is 0 or 1.

4. The inhibitor of claim 1 wherein n is 0, 1, or 2.

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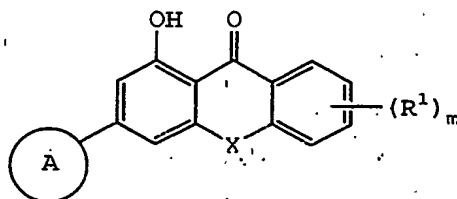
5. The inhibitor of claim 1 wherein X is selected from the group consisting of O, NH, NC(=O)-aryl, NC(=O)alkyl, and NC(=O)heteroaryl.

6. The inhibitor of claim 1 wherein R¹ is selected from the group consisting of halo, OR^d, OC₁₋₃alkyleneN(R^d)₂, heterocycloalkyl, substituted heterocycloalkyl, OC₁₋₃alkyleneC(=O)OR^d, N(R^d)C₁₋₃alkyleneN(R^d)₂, O(C₁₋₃alkylene)OP(=O)(OR^d)₂, O(C₁₋₃alkylene)OP(=O)(ONa)₂, OP(=O)(OR^d)₂, and OP(=O)(ONa)₂.

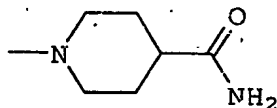
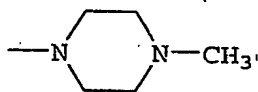
7. The inhibitor of claim 1 wherein n is 0, or R² is selected from the group consisting of OH, halo, CH₂OH, (C=O)NH₂, NH₂, OCH₃, NH(C=O)CH₃, NHCH₃, NO₂, O(CH₂)₁₋₃OH, O(C=O)heteroaryl, (C=O)aryl, O(C=O)alkyl, and OCH₂(C=O)CH₂aryl.

8. The inhibitor of claim 1 wherein Z is CH or C(OH).

9. The inhibitor of claim 1 having a structure



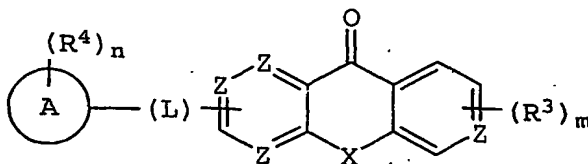
10. The inhibitor of claim 9 wherein m is 0 or R¹ is OCH₃, F,



X is O or NH; and A is morpholinyl.

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11. A DNA-PK inhibitor having a formula:



or a pharmaceutically acceptable salt thereof,

wherein m is an integer 0 through 3;

n is an integer 0 through 4;

X is O or NR^a ;

Z , independently, is CR^b or N;

L is selected from the group consisting of alkylene, substituted alkylene, carbonyl, carbamoyl, $-\text{NR}^d-$, $-\text{N}(\text{R}^d)_2$, $-\text{O}(\text{SO}_2)\text{R}^d$, $-\text{SO}_2\text{R}^d$, oxy ($-\text{O}-$), thio ($-\text{S}-$), thionyl ($-\text{SO}-$), and sulfonyl;

A is absent, or A is heteroaryl or a four- to seven-membered aliphatic ring containing 0, 1, 2, or 3 heteroatoms independently selected from the group consisting of N, O, and S;

R^1 , independently, is selected from the group consisting of halo, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, $\text{N}(\text{R}^d)_2$, OR^d , carboxyl, carboxy, nitro, $\text{OC}_{1-3}\text{alkyleneN}(\text{R}^d)_2$, $\text{N}(\text{R}^d)_{1-3}\text{alkyleneN}(\text{R}^d)_2$, $\text{OC}_{1-3}\text{alkyleneC}(=\text{O})\text{OR}^d$, $\text{O}(\text{C}_{1-3}\text{alkylene})\text{OP}(=\text{O})(\text{OR}^d)_2$, $\text{O}(\text{C}_{1-3}\text{alkylene})\text{OP}(=\text{O})-(\text{ONa})_2$, $\text{OP}(=\text{O})(\text{OR}^d)_2$, $\text{OP}(=\text{O})(\text{ONa})_2$, cyano, aldehyde,

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carboxamide, thiocarboxamide, acyl, mercapto, sulfonyl, trifluoromethyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or

two R^1 groups are taken together with the atoms to which each is attached to form a 5-, 6-, or 7-membered ring, wherein 1 or 2 carbon atoms of R^1 optionally is a heteroatom selected from the group consisting of O, N, and S, said ring optionally substituted with one or more of =O, =S, =NH, OR^c , $N(R^d)_2$, carboxyl, carboxy, alkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, and said heteroaryl optionally substituted with a substituent selected from the group consisting of aryl, substituted aryl, alkyl, substituted alkyl, and acyl;

R^2 , independently, is selected from the group consisting of OR^d , halo, $N(R^d)_2$, aldehyde, alkyl, substituted alkyl, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl C_{1-3} alkylene OR^d , $C(=O)N(R^d)_2$, $N(R^d)_2$, $(C=O)OR^d$, NO_2 , $NR^dC(=O)R^d$, $NR^d(SO_2)R^d$, $OC_{1-3}alkyleneOR^d$, $OC_{1-3}alkyleneOC_{1-3}alkyleneR^d$, $OC(=O)R^d$, $OC_{1-3}alkyleneC(=O)C_{1-3}alkyleneR^d$, and $(SO_3)R^d$;

R^a is selected from the group consisting of hydro, C_{1-4} alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $C_{1-3}alkylenearyl$, $C_{1-3}alkyleneheteroaryl$, $C_{1-3}alkyleneheterocycloalkyl$, $C_{1-4}alkyleneN(R^d)_2$, $C_{1-4}alkyleneOR^d$, $C_{1-4}alkyleneC(=O)OR^d$, $C(=O)R^d$,

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$C(=O)N(R^d)_2$, $C(=O)OR^d$, $C(=O)SR^d$, $C(=S)N(R^d)_2$, SO_2R^d , $SO_2N(R^d)_2$, $C(=O)NR^dC_{1-4}alkyleneOR^d$, $C(=O)NR^dC_{1-4}alkyleneheterocycloalkyl$, $C(=O)C_{1-4}alkylenearyl$, $C(=O)C_{1-4}alkyleneheteroaryl$, $C_{1-4}alkyleneC(=O)C_{1-4}alkylenearyl$, $C_{1-4}alkyleneC(=O)C_{1-4}alkyleneheteroaryl$, $C_{1-4}alkyleneC(=O)heterocycloalkyl$, $C_{1-4}alkyleneNR^dC(=O)R^d$, $C_{1-4}alkyleneOC_{1-4}alkyleneOR^d$, $C_{1-4}alkyleneOC_{1-4}alkyleneC(=O)OR^d$, and $C_{1-4}alkyleneC(=O)N(R^d)_2$;

R^b , independently, is selected from the group consisting of hydro, alkyl, halo, aldehyde, OR^d , $O(C_{1-3}alkylene)OP(=O)(OR^d)_2$, $O(C_{1-3}alkylene)OP(=O)(ONa)_2$, $OP(=O)(OR^d)_2$, $OP(=O)(ONa)_2$, nitro, $N(R^d)_2$, carboxyl, carboxy, sulfonamido, sulfamyl, and sulfo or a halide derivative thereof; and

R^d , independently, is selected from the group consisting of hydro, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, $C_{1-3}alkylenearyl$, substituted aryl, heteroaryl, and substituted heteroaryl.

12. The inhibitor of claim 11 wherein A is absent.

13. The inhibitor of claim 11 wherein A is selected from the group consisting of pyridyl, morpholinyl, piperazinyl, thiomorpholinyl, piperidinyl, and tetrahydropyranyl.

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14. The inhibitor of claim 11 wherein m is 0 or 1.

15. The inhibitor of claim 11 wherein n is 0, 1, or 2.

16. The inhibitor of claim 11 wherein X is selected from the group consisting of O, NH, NC(=O)aryl, NC(=O)alkyl, and NC(=O)heteroaryl.

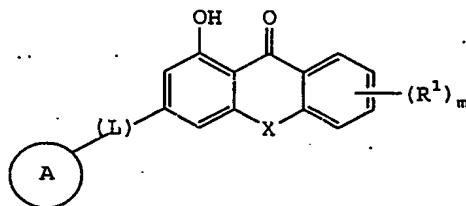
17. The inhibitor of claim 11 wherein R¹ is selected from the group consisting of halo, OR^d, OC₁₋₃alkyleneN(R^d)₂, heterocycloalkyl, substituted heterocycloalkyl, OC₁₋₃alkyleneC(=O)OR^d, N(R^d)C₁₋₃alkyleneN(R^d)₂, O(C₁₋₃alkylene)OP(=O)(OR^d)₂, O(C₁₋₃alkylene)OP(=O)(ONa)₂, OP(=O)(OR^d)₂, and OP(=O)(ONa)₂.

18. The inhibitor of claim 11 wherein R² is selected from the group consisting of OH, halo, CH₂OH, (C=O)NH₂, NH₂, OCH₃, NH(C=O)CH₃, NHCH₃, NO₂, O(CH₂)₁₋₃OH, O(C=O)heteroaryl, (C=O)aryl, O(C=O)alkyl, and OCH₂(C=O)CH₂aryl.

19. The inhibitor of claim 11 wherein Z is CH, C(OH), COCH₂CH₂OP(=O)(OCH₂C₆H₅)₂, COCH₂CH₂OP(=O)(ONa)₂, OP(=O)(OCH₂C₆H₅)₂, and OP(=O)(ONa)₂.

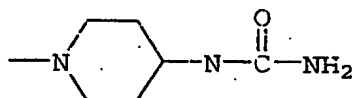
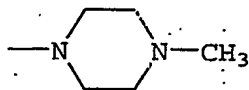
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20. The inhibitor of claim 11 having a structure



and prodrugs thereof.

21. The inhibitor of claim 19 wherein m is 0 or R¹ is OCH₃, F,



X is O or NH; and A is absent.

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22. A DNA-PK inhibitor selected from the group consisting of:

trifluoromethanesulfonic acid 1-hydroxy-9-oxo-9H-xanthen-3-yl ester;

1-hydroxy-3-morpholin-4-yl-xanthen-9-one;

1-hydroxy-6-methoxy-3-trifluoromethanesulfonylxanthen-9-one ester;

1-hydroxy-6-methoxy-3-morpholin-4-yl-xanthen-9-one;

6-fluoro-1-hydroxy-3-morpholin-4-yl-xanthen-9-one;

1-hydroxy-6-(4-methylpiperazin-1-yl)-3-morpholin-4-yl-xanthen-9-one;

1-(8-hydroxy-6-morpholin-4-yl-9-oxo-9H-xanthen-3-yl)-piperidine-4-carboxylic acid amide;

trifluoromethanesulfonic acid 1-hydroxy-9-oxo-9,10-dihydro-acridin-3-yl ester; and

1-hydroxy-3-morpholin-4-yl-10H-acridin-9-one.

23. A pharmaceutical composition comprising (a) DNA-PK inhibitor claim 1 or claim 11, and (b) a pharmaceutically acceptable carrier or diluent.

24. A pharmaceutical composition comprising (a) a DNA-PK inhibitor of claim 1 or 11, and (b) an antineoplastic agent.

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25. The pharmaceutical composition of claim 24, wherein A is morpholinyl, L is absent, R^1 and R^2 are hydrogen, and Z is CH at each occurrence.

26. The pharmaceutical composition of claim 24 wherein L is absent, or L is selected from the group consisting of $-NR^d$ -, and $-S$ -;

A is absent, or is selected from the group consisting of morpholinyl, piperazinyl, thiomorpholinyl, piperidinyl, and tetrahydropyranyl;

m is 0 or 1, or R^1 is selected from the group consisting of halo, OR^d , $OC_{1-3}alkyleneN(R^d)_2$, heterocycloalkyl, substituted heterocycloalkyl, $OC_{1-3}alkyleneC(=O)OR^d$, $N(R^d)C_{1-3}alkyleneN(R^d)_2$, $OP(=O)(OR^d)_2$, and $OP(=O)(ONa)_2$; and

n is 0, 1, or 2, or R^2 is selected from the group consisting of OH, halo, CH_2OH , $(C=O)NH_2$, NH_2 , OCH_3 , $NH(C=O)CH_3$, $NHCH_3$, NO_2 , $O(CH_2)_{1-3}OH$, $O(C=O)heteroaryl$, $(C=O)aryl$, $O(C=O)alkyl$, and $OCH_2(C=O)CH_2aryl$.

27. The pharmaceutical composition of claim 24 wherein the antineoplastic agent comprises a chemotherapeutic agent or a radiotherapeutic agent.

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28. The pharmaceutical composition of claim 27 wherein the antineoplastic agent is selected from the group consisting of an alkylating agent, an antimetabolite, a type I topoisomerase inhibitor, an antimitotic drug, an antibiotic, an enzyme, a biological response modifier, a differentiation agent, and a radiosensitizer.

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29. The pharmaceutical composition of claim 27 wherein the antineoplastic agent is selected from the group consisting of mechlorethamine, cyclophosphamide, ifosfamide, melphalan, carmustine, chlorambucil, lomustine, semustine, thriethylene-melamine, triethylene thiophosphoramide, hexamethylmelamine, busulfan, dacarbazine, methotrexate, trimetrexate, 5-fluorouracil, fluorodeoxyuridine, gemcitabine, cytosine arabinoside, 5-azacytidine, 2,2-difluorodeoxycytidine, 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin, erythrohydroxynonyladenine, fludarabine phosphate, 2-chlorodeoxyadenosine, camptothecin, topotecan, irinotecan, paclitaxel, vinblastine, vincristine, vinorelbine, docetaxel etoposide, teniposide, actinomycin D, daunomycin, doxorubicin, mitoxantrone, idarubicin, bleomycin, plicamycin, mitomycin C, dactinomycin, L-asparaginase, interferon-alpha, IL-2, G-CSF, GM-CSF, metronidazole, misonidazole, desmethylmisonidazole, pimonidazole etanidazole, nimorazole, RSU 1069, EO9, RB 6145, SR4233, nicotinamide, 5-bromodeoxyuridine, 5-iododeoxyuridine, bromodeoxycytidine, cisplatin, carboplatin, mitoxantrone, hydroxyurea, N-methylhydrazine, procarbazine, mitotane, aminoglutethimide, prednisone, dexamethasone, hydroxyprogesterone caproate, hydroxyprogesterone acetate, megestrol acetate, diethylstilbestrol ethynyl estradiol, tamoxifen, testosterone

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propionate, fluoxymesterone, flutamide, leuprolide, flutamide, tin etioporphyrin, pheoboride-a, bacteriochlorophyll-a, a naphthalocyanine, a phthalocyanine, and a zinc phthalocyanine.

30. A method of inhibiting DNA-PK activity comprising the step of contacting a DNA-PK with a DNA-PK inhibitor of claim 1 or 11.

31. A method of sensitizing a cell type to an agent that induces DNA lesions comprising the step of contacting the cell type with a compound of claim 1 or 11.

32. The method of claim 31 wherein the agent that induces DNA lesions is selected from the group consisting of radiation, an exogenous chemical, a metabolite by-product, and mixtures thereof.

33. A method of potentiating a therapeutic regimen for treatment of a cancer comprising the step of administering to an individual in need thereof an effective amount of a DNA-PK inhibitor of claim 1 or 11.

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34. The method of claim 33 wherein the therapeutic regimen for treatment of cancer is selected from the group consisting of chemotherapy, radiation therapy, and a combination of chemotherapy and radiation therapy.

35. A method of characterizing the potency of a test compound as an inhibitor of a DNA-PK polypeptide, said method comprising the steps of:

- a) measuring an activity of a DNA-PK polypeptide in the presence of a test compound;
- b) comparing the activity of the DNA-PK polypeptide in the presence of the test compound to the activity of the DNA-PK polypeptide in the presence of an equivalent amount of a reference compound of claim 1 or 11, wherein a lower activity of the DNA-PK polypeptide in the presence of the test compound than in the presence of the reference compound indicates that the test compound is a more potent inhibitor than the reference compound, and a higher activity of the DNA-PK polypeptide in the presence of the test compound than in the presence of the reference compound indicates that the test compound is a less potent inhibitor than the reference compound.

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36. A method of characterizing the potency of a test compound as an inhibitor of a DNA-PK polypeptide, said method comprising the steps of:

a) determining an amount of a control compound of claim 1 or 11 that inhibits an activity of a DNA-PK polypeptide by a reference percentage of inhibition, thereby defining a reference inhibitory amount for the control compound;

b) determining an amount of a test compound that inhibits an activity of a DNA-PK polypeptide by a reference percentage of inhibition, thereby defining a reference inhibitory amount for the test compound;

c) comparing the reference inhibitory amount for the test compound to a reference inhibitory amount determined according to step (a) for the control compound, wherein a lower reference inhibitory amount for the test compound than for the control compound indicates that the test compound is a more potent inhibitor than the control compound, and a higher reference inhibitory amount for the test compound than for the control compound indicates that the test compound is a less potent inhibitor than the control compound.

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37. The method of claim 36 wherein the method comprises determining the reference inhibitory amount of the test compound in an *in vitro* biochemical assay.

38. The method of claim 37 wherein the method comprises determining the reference inhibitory amount of the test compound in an *in vitro* cell-based assay.

39. The method of claim 36 wherein the method comprises determining the reference inhibitory amount of the test compound in an *in vivo* assay.

40. An article of manufacture comprising:

- a) an anticancer compound that induces double-strand DNA breakage in cells; and
- b) a package insert describing a coordinated administration to a patient of said anticancer compound and a DNA-PK inhibitor compound of claim 1 or 11.

41. The article of manufacture according to claim 40 wherein said anticancer compound induces DNA double strand breaks.

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42. The article of manufacture according to claim 40 wherein the anticancer compound is selected from the group consisting of bleomycin and etoposide.

43. An article of manufacture comprising:

- a) a compound selected from the group consisting of a cytokine, a lymphokine, a growth factor, and a hematopoietic factor; and
- b) a package insert describing a coordinated administration to a patient of said compound and a DNA-PK inhibitor compound of claim 1 or 11.

44. An article of manufacture comprising:

- a) a pharmaceutical composition comprising a DNA-PK inhibitor of claim 1 or 11 in a pharmaceutically acceptable carrier; and
- b) a package insert describing a therapeutic treatment comprising administering the DNA-PK inhibitor.

45. An article of manufacture comprising:

- a) a pharmaceutical composition comprising a DNA-PK inhibitor of claim 1 or 11 in a pharmaceutically acceptable carrier; and
- b) a package insert describing a therapeutic treatment comprising administering the DNA-PK inhibitor.